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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,992	ASHKENAZI, ET AL	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-46 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-46 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5/27/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 5/27/03, in which changes were made to the specification (e.g. to remove hyperlinks and complete biological deposit information), and in which several claims were amended (claims 39-44) and claims were cancelled (claims 47-48). Claims 39-46, 49-51 are pending and under consideration. This action is FINAL.

Information Disclosure Statement (IDS)

Receipt is acknowledged of a supplemental IDS filed on 5/27/03. Only the three references cited on the PTO Form 1449 that are present in the file were actually considered. If applicants wish the other references to be considered, it will be necessary to file an additional IDS along with the cited references.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 39-46, 49-51 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. **This rejection is maintained for reasons of record in the office action mailed 2/26/2003, which grounds are repeated below.**

Each of the claims is directed towards an isolated protein having at least 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the polypeptide shown in Figure 90 (SEQ ID NO: 255 or PRO302). In addition, or alternatively, the rejected claims read on a protein having

80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to SEQ ID NO: 255, but lacking its associated signal peptide. The isolated polypeptide can have 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the extracellular domain of SEQ ID NO: 255. The isolated polypeptide can have 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the extracellular domain of SEQ ID NO: 255, but lacking the associated signal peptide. In addition, the isolated polypeptide can have 80%, 85%, 90%, 95%, 99% or 100% amino acid sequence identity to the protein encoded by the coding sequence of ATCC deposit number 209485. The isolated protein can be a chimeric protein comprising the polypeptide of the invention fused to a heterologous peptide sequence (e.g. an epitope tag or an Fc region of an immunoglobulin.

SEQ ID NO: 255 appears to have been novel in the art at the time of filing. Likewise, the nucleic acid sequence disclosed by applicants as encoding SEQ ID NO: 255, SEQ ID NO: 254, likewise appears to be novel in the art. Therefore, there is no well-established utility for the claimed proteins.

The specification asserts that, based upon BLAST and FastA sequence analysis, various portions of PRO302 have significant homology with various protease proteins (page 110, top paragraph). Exactly which portions have homology to which portions of which other known proteases is not taught, however. Based upon the assertion that PRO302 comprises proteolytic activity, the specification asserts that PRO302 has utility in vivo for therapy as well as in vitro utilities. There is no indication in the specification that the supposed protease has any *specific* target for its supposed activity (e.g. association with a particular disease or specific substrate).

It is not likely that one of skill in the art could reasonably predict based upon the primary sequence of SEQ ID NO: 255 what specific activity PRO302 may have. The relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its activity), is not well understood and is not predictable as evidenced by Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and failures to make it predictable. Thus, as taught by Berendsen, it is unlikely that one could predict the structural/functional characteristics of PRO302 based upon primary sequence alone. Further supporting Berendsen's teachings, Galparin et al (Nature Biotechnology, Vol. 18, pages 609-613, June 2000; see the entire reference) teach that "sequence comparison methods, even the best ones, are of little help when a protein has no homologs in current databases or when all database hits are to uncharacterized gene products." Galperin et al disclose that "assessing the actual power of the context based method for protein function prediction requires extensive testing by labor-consuming, case-by-case, computational, and eventually experimental analysis." Attwood (Science, Vol. 290, pages 471-473, see the entire reference) also states that it is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." It is clear from the cited references that one cannot reliably predict based upon primary structure alone or on mere sequence homology what specific activity PRO302 might possess.

The specification does teach in Example 85 that the PRO302 protein has an effect on vascular leakage when injected into hairless guinea pigs. While the specification concludes that PRO302 protein can induce vascular permeability in the guinea pig model, it does not give the actual data or an indication of the relative activity of the PRO302 protein compared to the positive control. In addition to not providing a basis for one of skill in the art to determine the actual effectiveness of PRO302 in inducing vascular permeability, the specification does not provide a basis to envision a specific, real-world application for the asserted ability to induce vascular permeability. It is further noted that the observed activity is not unique to PRO302 in that at least one other protein and the positive control both induced vascular permeability in the guinea pig model. Based on these teachings, one of skill in the art at the time of applicants' invention would not be able to recognize a specific utility (e.g. specific proteolytic substrate) or substantial utility (i.e. not requiring additional research in order to confirm a real-world application for the claimed proteins) for the claimed proteins.

Claims 39-51 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Arguments

Applicant's arguments filed on 5/27/03 have been fully considered but they are not persuasive. The response essentially argues: 1) the patent office is not the FDA and should not apply its standards, 2) the assertion that the claimed invention is useful is credible, 3) the results of the vascular leak assay of Example 85 are sufficient to establish a specific, substantial and

credible utility for the protein to which the claimed antibodies bind (i.e. PRO302 described by SEQ ID NO: 255), 4) PRO302 was demonstrated to increase skin vascular permeability, 5) such assays are known and used in the art to correlate such activity with disease and/or evaluate the vascular permeabilizing function of a given substance (e.g. the Wei et al, Wise et al and Collins et al references), 5) vascular permeabilization can occur during wound healing or in pathological conditions such as tumor formation, 6) just as VPF (alternatively known as VEGF; see the Collins et al reference) has been shown to play a role in many important biological functions, a variety of real-life utilities are envisioned for PRO302 base on the results of Example 85 (e.g. PRO302 could be used to induce wound healing), 7) antibodies raised against PRO302 could be used to diagnose target tissue disorders (e.g. tumor formation), 8) working Example 85 provides a positive control (human VEGF) and PRO302 tested positive in the assay (i.e. response greater than 5-7 mm in diameter), 9) the fact that other proteins may induce such a response is irrelevant for utility considerations, 10) applicants' assertion that PRO302 is an inducer of vascular permeability would be recognized by the skilled artisan as a credible assertion.

At no point in making the rejection did the examiner state that applicants' assertions concerning any utility for PRO302 were not credible (e.g. in the sense of claiming a perpetual motion machine). Rather, the grounds for the rejection are made along the lines of a lack of a specific and substantial utility. The results Example 85 do not support a specific or substantial utility. No specific disease or condition was shown to be correlated with the presence and/or expression of PRO302. Nor has it been shown that PRO302 has any effect, naturally or otherwise, on wound healing. The mere fact that PRO302 may have an effect on vascular permeabilization is not sufficient grounds for one of skill in the art to assume that it can be used

in wound healing and/or diagnosis of a particular disease or condition. Moreover, the examiner cannot determine the *degree* to which PRO302 had any affect on vascular permeabilization. For example, while it is true that applicants did provide a "positive control" of sorts for Example 85 by using VEGF (producing a response of 15-23 mm), the statement that PRO302 tested positive merely means that, by applicants' standards, PRO302 produced a response of >5-7 mm depending on the assay. The exact degree of response observed (e.g. as compared to VEGF) is not described in the specification, making it difficult to determine just how effective PRO302 is at inducing permeability. Neither applicants' response nor the references cited in their response indicate that PRO302 would necessarily have the asserted utilities. The skilled artisan would reasonably have concluded at the time of filing that the claimed invention lacks a specific (i.e. particular proteolytic substrate, or correlation to a particular disease or condition) or substantial (i.e. not requiring additional experimentation to identify and confirm a real world use) utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following enablement rejection is provided in the event that the rejection outlined above under 35 U.S.C. 101 for lack of a specific and substantial or well-established utility is overcome. While it may be possible that applicants can demonstrate that the instant specification and/or prior art provides a specific and substantial or well-established utility for the claimed

proteins, there remain other grounds for rejecting the instant claims under 35 U.S.C. 112 1st for lack of enablement. These additional grounds are outlined below.

Claims 39-46, 49-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record in the office action mailed 2/26/2003, which grounds are repeated below.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The nature of the invention is complex, involving the use of proteins without a well-defined function.

Breadth of the claims: The complexity of the invention is exacerbated by the great breadth of the claims, encompassing proteins with as little as 80% identity to SEQ ID NO: 255, or portions thereof (e.g. a purported extracellular domain). This includes a very large number of proteins that do not possess the specific activity of PRO302 and for which the specification provides no teachings as to a real-world use.

Guidance of the specification: The specification teaches that the cDNA encoding PRO302 was obtained from a human fetal kidney RNA library that was probed with oligomers

designed from a putative extracellular domain for a given protein (e.g. Example 1, Example 85). The specification asserts that, based upon BLAST and FastA sequence analysis, various portions of PRO302 have significant homology with various protease proteins (page 110, top paragraph). Exactly which portions have homology to which portions of which other known proteases is not taught, however. Nor is it taught what exactly are the functional domains within the PRO302 polypeptide. Based upon the assertion that PRO302 comprises proteolytic activity, the specification asserts that PRO302 has utility in vivo for therapy as well as in vitro utilities. There is no teaching in the specification that the supposed protease has any *specific* target for its supposed activity (e.g. association with a particular disease or specific substrate). The specification does teach in Example 85 that the PRO302 protein has an effect on vascular leakage when injected into hairless guinea pigs. While the specification concludes that PRO302 protein can induce vascular permeability in the guinea pig model, it does not give the actual data or an indication of the relative activity of the PRO302 protein compared to the positive control. In addition to not providing a basis for one of skill in the art to determine the actual effectiveness of PRO302 in inducing vascular permeability, the specification does not provide a basis to envision a specific, real-world application for the asserted ability to induce vascular permeability.

The existence of working examples: The only working example for PRO302 is the experiment wherein it was purportedly shown that PRO302 can induce some unspecified degree of vascular permeability in the guinea pig.

State of the art/Predictability of the art: It is not likely that one of skill in the art could reasonably predict based upon the primary sequence of SEQ ID NO: 255 what specific activity

PRO302 may have. The relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its activity), is not well understood and is not predictable as evidenced by Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and failures to make it predictable. Thus, as taught by Berendsen, it is unlikely that one could predict the structural/functional characteristics of PRO302 based upon primary sequence alone.

Further supporting Berendsen's teachings, Galparin et al (Nature Biotechnology, Vol. 18, pages 609-613, June 2000; see the entire reference) teach that "sequence comparison methods, even the best ones, are of little help when a protein has no homologs in current databases or when all database hits are to uncharacterized gene products." Galperin et al disclose that "assessing the actual power of the context based method for protein function prediction requires extensive testing by labor-consuming, case-by-case, computational, and eventually experimental analysis." Attwood (Science, Vol. 290, pages 471-473, see the entire reference) also states that it is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences." It is clear from the cited references that one cannot reliably predict based upon primary structure alone or on mere sequence homology what specific activity PRO302 might possess. Therefore, determining how to use the claimed polypeptides, even those having

the same activity as determined for the protein described by SEQ ID NO: 255 would have been unpredictable at the time of filing.

The amount of experimentation necessary: Given the combination of factors outlined above, it would have required undue, unpredictable experimentation for one of skill in the art to use the claimed polypeptides. For example, in order to determine whether the a polypeptide meeting the claim limitations of a given percent identity to SEQ ID NO: 255, or portions thereof, has a particular activity one would have to envision an appropriate assay and conditions for measuring the purported activity. With proteolytic activity, one of skill in the art would have to envision which possible substrate of all the possible protein substrates available and under which conditions would be likely to result in an observation of the supposed activity. One would then have to envision the appropriate reaction conditions for performing the assay (e.g. purified or unpurified protein, temperature, buffer conditions, possible co-factors, etc.). If unsuccessful in determining an activity for the claimed protein, which is likely given the combination of factors outlined above and the unpredictability of the art, one of skill in the art would then have to envision a change to the first assay conditions (e.g. different substrate, buffer composition, temperature, duration and/or completely different assay) and repeat the entire unpredictable process. Thus, it would require undue, unpredictable experimentation for one of skill in the art to use the claimed proteins having a specified percent identity to PRO302 (SEQ ID NO: 255). Therefore, the instant specification is not considered to be enabling for the use of any of the claimed proteins.

Response to Arguments

Applicant's arguments filed on 5/27/03 have been fully considered but they are not persuasive. The response essentially argues: 1) the amendment of the claims to include the functional limitation "wherein said polypeptides are capable of enhancing vascular permeability" should overcome the enablement rejection, 2) due to the general knowledge in the art at the time of filing, the skilled artisan knew how to make and use the claimed invention, and 3) just because experimentation is complex does not make it undue.

With regard to claims directed to the protein described by SEQ ID NO: 255, the rejection of these claims for lack of enablement will be maintained at least until such time as applicants have overcome the utility rejection set forth above. Even in the event that applicants can make a convincing argument that Pro302 has met the utility standard for 35 U.S.C. 101 based upon a specific and substantial utility featuring vascular permeabilization (e.g. Example 85), there is still the need to satisfy the requirements of 35 U.S.C. 112 for the protein identified by applicants. As indicated above, no specific proteolytic target has been identified for the protein. With regard to vascular permeabilization activity and use of the protein for various treatments similar to VEGF (e.g. wound healing, etc.), there is no guidance in the specification as to how Pro302 is functioning to increase vascular permeabilization in the animal model. There is, for example, no evidence or teaching in the prior art or specification that Pro302 functions biochemically in a manner similar to that for VEGF. Thus, one cannot simply rely upon the teachings in the prior art for VEGF as a reliable road map for using Pro302. Any experimentation towards this end would necessarily be unpredictable, trial-and-error experimentation and would, given the lack of guidance from the prior art and specification as to how to use the claimed protein, be undue.

With regard to arguments directed to the new functional limitation of the claims, even if one concedes that the protein described by SEQ ID NO: 255 has utility due to the observed vascular permeabilization activity and that the "wildtype" protein is enabled by the instant specification for some use (neither of which is conceded here), there are no teachings at all in the specification or prior art as to what portions or amino acid residues within the protein are required for the effect of increasing vascular permeabilization. Thus, in order to make and use the claimed invention with proteins other than the protein used in Example 85 (e.g. proteins with only 80%, 90%, 99% identity to SEQ ID NO: 255), it would require undue, unpredictable experimentation in order to identify those variants of SEQ ID NO: 255 that retain the recited functional activity.

Claims 39-44, 47-48, 50-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection, necessitated by applicant's amendment of the claims in the response filed 5/27/03.**

Each of the rejected claims is directed to a protein comprising a specified percent identity (e.g. 80%, 85%, 90%, 95% and 99%) to SEQ ID NO: 255, where the protein must necessarily be capable of enhancing vascular permeability. The protein described by SEQ ID NO: 255 is 452 amino acids in length. Thus, the claims encompass a large number of sequence variants of the protein described by SEQ ID NO: 255 that must retain the ability to enhance vascular permeability in an organism.

There is no discussion in the prior art or instant specification concerning the domains or specific amino acid residues that are responsible for the vascular permeabilization activity recited in the rejected claims. Therefore, there is no basis for the skilled artisan to envision a sufficient number of specific embodiments of the protein variants to describe the broadly claimed genus of such proteins that retain the ability to enhance vascular permeability in an organism.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER

Ggl